

FNL Operations and Update

Frederick National Laboratory
for Cancer Research

sponsored by the National Cancer Institute



Ethan Dmitrovsky, M.D.

**President, Leidos Biomedical Research and Laboratory
Laboratory Director, Frederick National Laboratory for Cancer Research**

DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health • National Cancer Institute

Frederick National Laboratory is a Federally Funded Research and Development Center operated by Leidos Biomedical Research, Inc., for the National Cancer Institute

Session Objectives

- 1. Update Frederick National Laboratory rapid response to the Omicron variant and pandemic.**
- 2. Show how these actions did not disrupt operations or delay quantitative, discovery, translational or clinical science.**
- 3. Describe NCI and NIAID projects that exemplify federally-funded research and development efforts and how we share our expertise with extramural community.**
- 4. Answer your questions.**

Federally Funded Research and Development Center (FFRDC) Operations

This contract works through a Task Order portfolio:

- **5 Operational Task Orders - Benefits of services are recurring with annual funded appropriations.
(NCI Task Order, 3 NIAID Task Orders, 1 Lease Task Order)**
- **103 are Non-operational Task Orders**
- **69 are in the Clinical Group**
- **16 are in the Scientific Group**
- **18 are Facility or Infrastructure Refurbishments Task Orders**

Extensive outreach to the broader research community is through subcontracting.

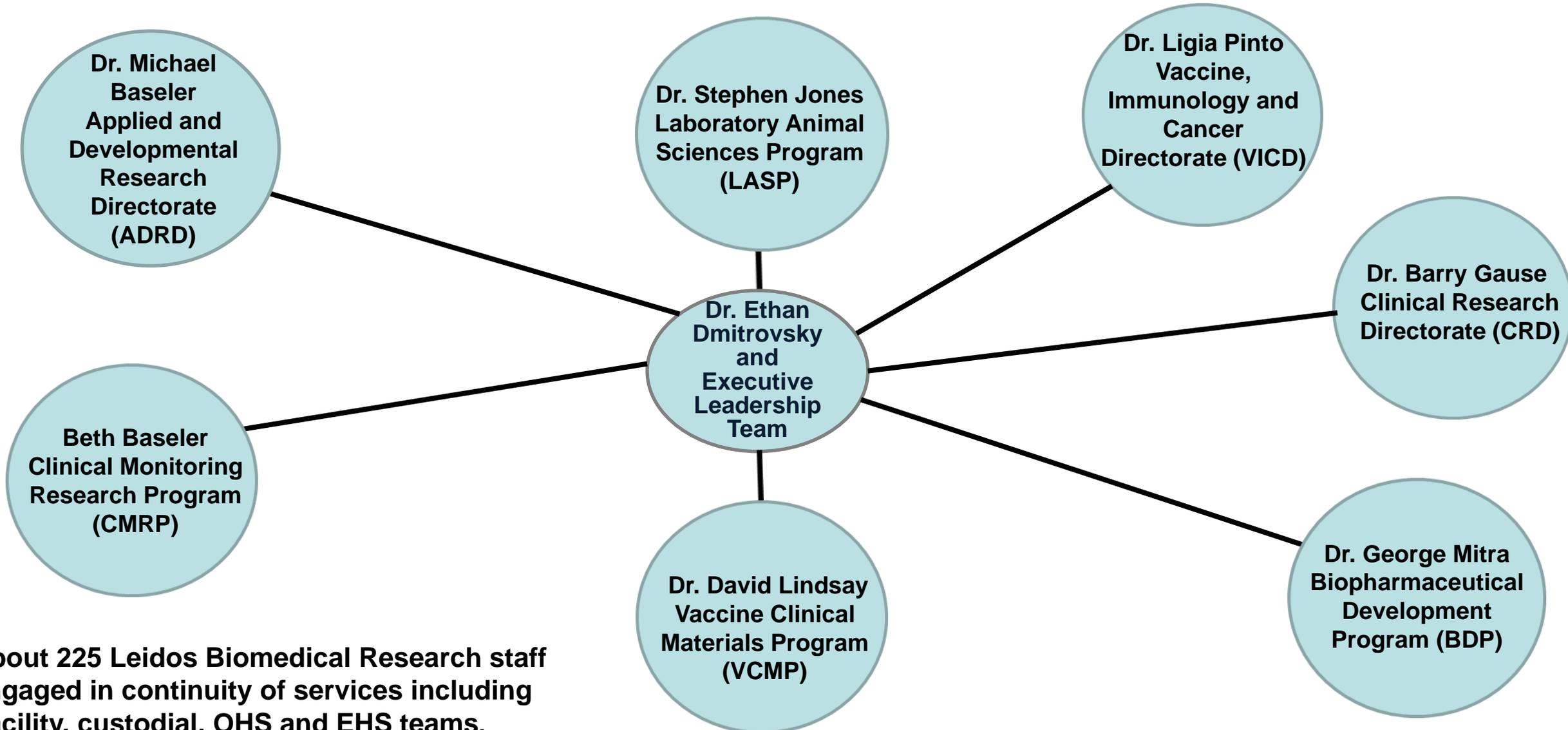
Frederick National Laboratory for Cancer Research (Case Study of Rapid Response)

International



Fire and looting at the C.H. Rennie Hospital research and clinical care site in Liberia (see Baltimore Sun and STAT News commentaries about public-private partnerships by E. Dmitrovsky)

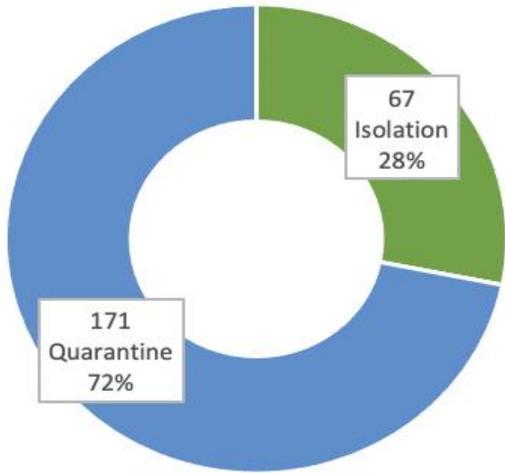
Continuity of Veterinary, Scientific and Clinical Services During the Pandemic



About 225 Leidos Biomedical Research staff engaged in continuity of services including Facility, custodial, OHS and EHS teams.

Frederick National Laboratory Rapid Response to COVID-19 Delta and Omicron Variants

Omicron was 56% of isolation or positive test cases tracked by Occupational Health Services.

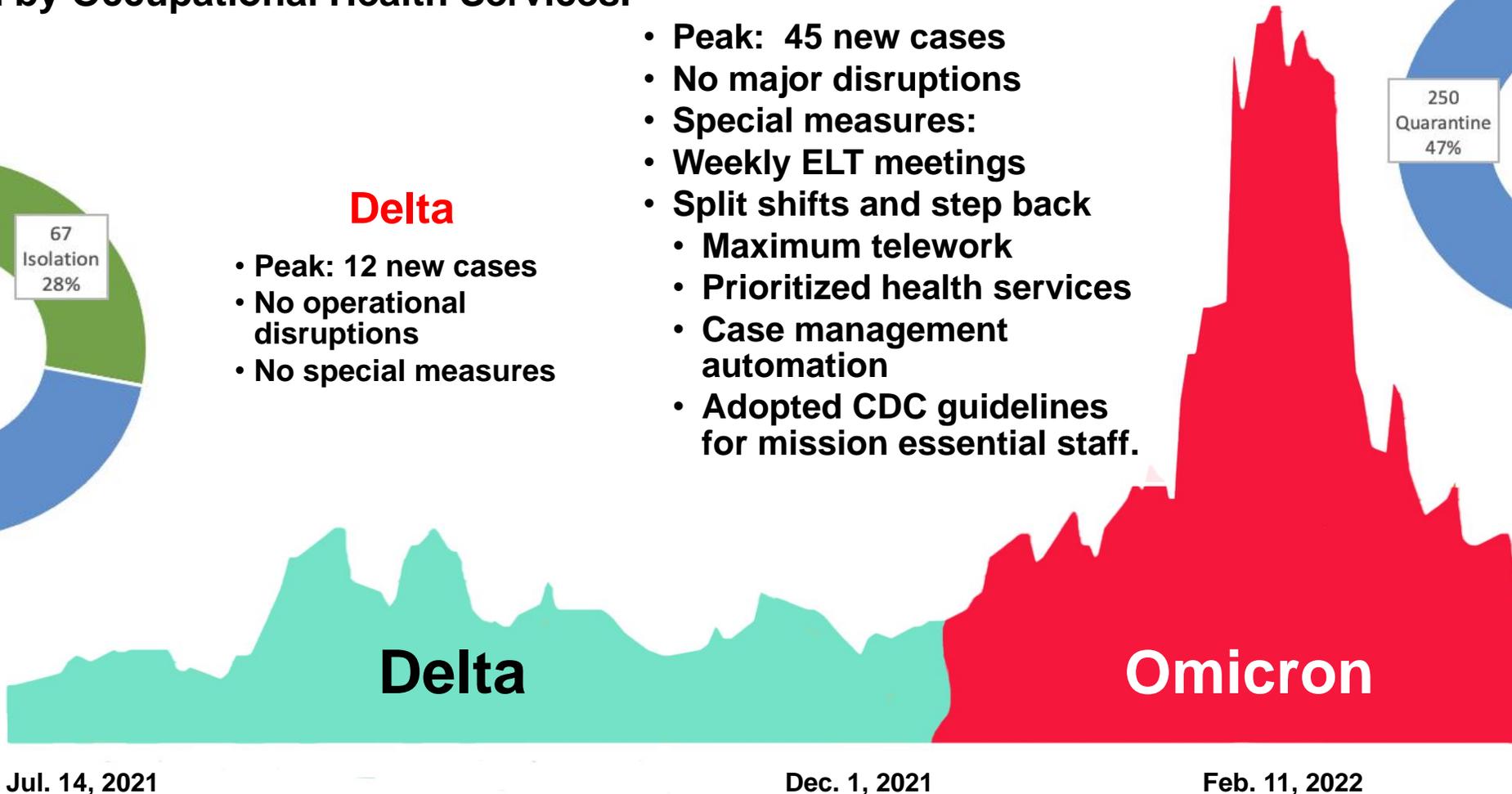
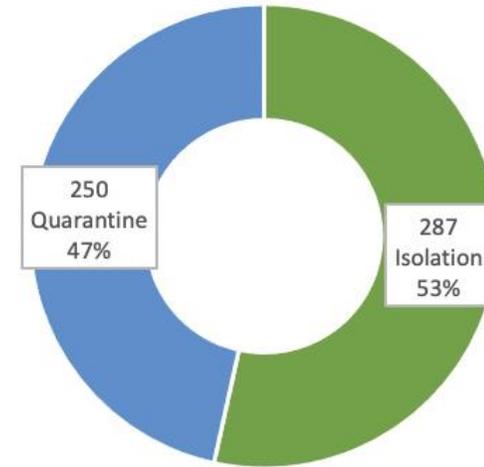


Delta

- Peak: 12 new cases
- No operational disruptions
- No special measures

Omicron

- Peak: 45 new cases
- No major disruptions
- Special measures:
 - Weekly ELT meetings
 - Split shifts and step back
 - Maximum telework
 - Prioritized health services
 - Case management automation
 - Adopted CDC guidelines for mission essential staff.



Delta

Omicron

Operations Teams Optimize Support of Science and Medical Missions

Frederick National Laboratory

Science & Technology
Group

Clinical Group

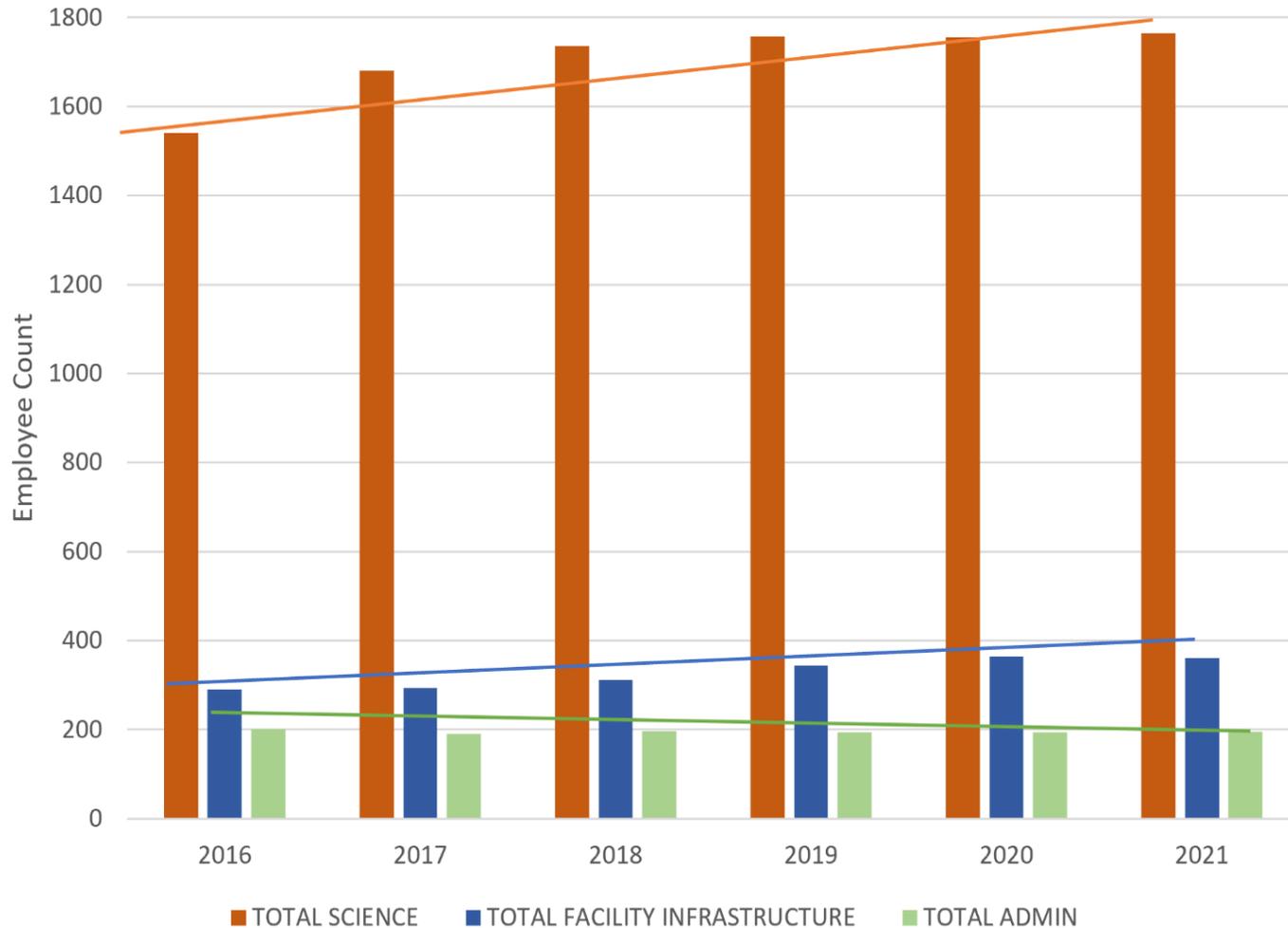


The Operations Group exists to support the research at Frederick National Laboratory for Cancer Research.

- The Operations Group maintains a mindset and culture of service.
- Structured to achieve minimal administrative burden.
- Models vigilance in process review, refinement, and continuous improvement.
- **Case study:**
Update the NIH Enterprise Directory (NED).

Operations Team Puts Science First

Annual Headcount By Function



Cost on contract grew by **19%**
Science staff grew by **12.4%**
Facility/Infrastructure staff grew by **12.7%**
Administrative staff decreased by **6.5%**

Administrative costs controlled by:
Some positions not back-filled. Some staff promoted, adding to leadership diversity.
Rigorous refinement of processes.
Shifted or removed roles for efficiency.
Leveraged IT resources.

Investments made in the
well-being of our staff.



SeroNet Permanent Space (6 month reduction in refurbishment time)

Relocate Program into a single space.

Most of one floor will be refurbished to consolidate the SeroNet Initiative Program groups under the Vaccine, Immunity and Cancer Directorate into one space, relocating the Program groups from multiple other locations.

Refurbishment is in phases. The first relocates current occupants and minimizes effects on scientific operations of other groups.



SeroNet Space

United States SARS-CoV-2 Serology Standard

A tool to enable serology assay harmonization and to increase comparability of results from different serology studies. (Calibrated against the WHO International Standard, IU/mL)

Entity	US Standard Requests	Evaluation Panel Requests
Pharma/Biotech	56	4
US Government	13	2
SeroNet	29	12
Academic	32	1
Other	8	0
TOTAL	138	19

SeroNet Members – [SeroNet Reagent Request Form](#) on MS Teams

Non-SeroNet Members – <https://frederick.cancer.gov/initiatives/seronet/serology-standard>

Support for NCI CAR-T Cell Trials

With the Division of Cancer Treatment and Diagnosis (DCTD)

Phased Clinical Trial Approach

Pediatric AML (CD33)

Manufactured by Biopharmaceutical Development Program (BDP)
Trials with National Marrow Donor Program (NMDP)
18 enrolled, 14 treated (7 at NCI, 5 at CHOP, 2 others)

Pediatric Neuroblastoma/Osteosarcoma (GD2)

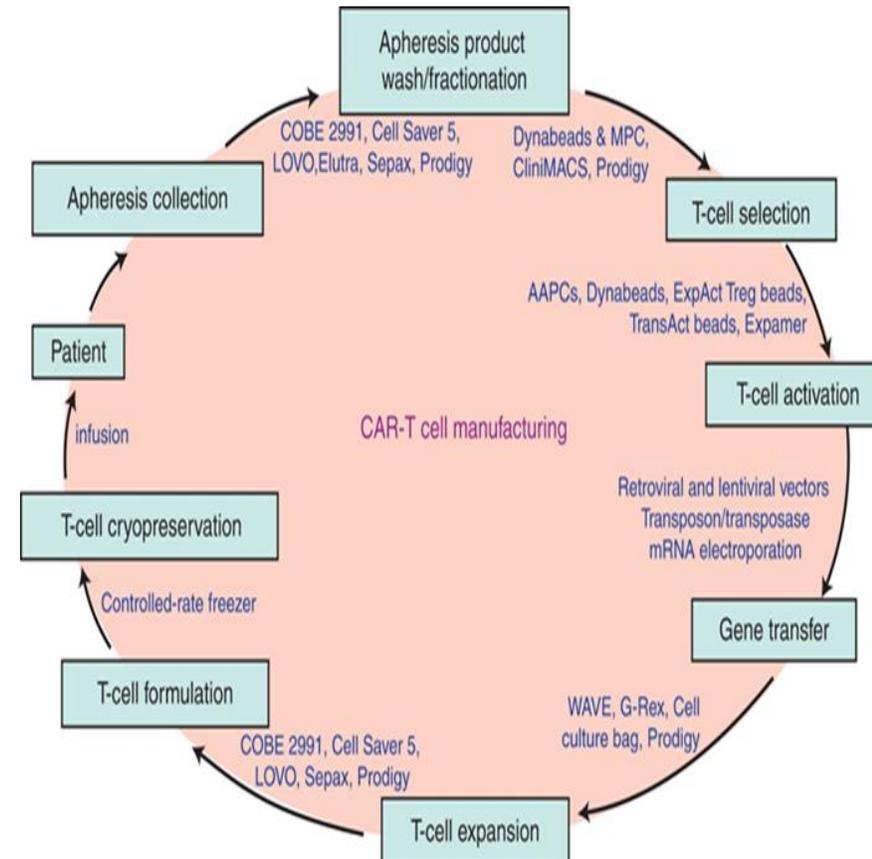
Manufacture at BDP
Open at Clinical Center and Stanford in February, 2022
Expand to Children's Immuno-Therapy Network (CITN)

Planned

HYP218 CART (Mesothelin) - mesothelioma, ovarian, pancreatic lung adenocarcinoma and cholangiocarcinoma (Q4 2022)
GPC2 CART – Neuroblastoma
STEAP1 CART – Prostate cancer

CART Gene Transfer at BDP

Lentiviral Vector is current technology
CRISPR-Cas 9 knock in/out under development



Dr. Sharpless
Dr. James Doroshow
Dr. Kristin Komschlies
Dr. Anthony Welch
Dr. Jason Yovandich
Dr. Barry Gause
Dr. George Mitra
Joy Beveridge

Prodigy System

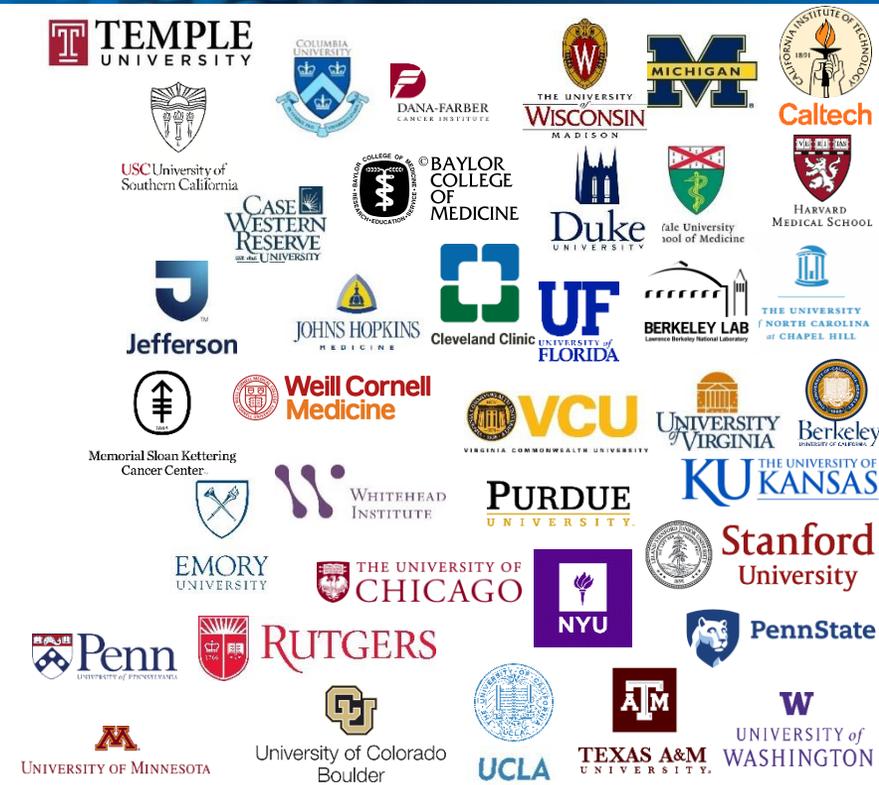


NCI National Cryo-Electron Microscopy Facility

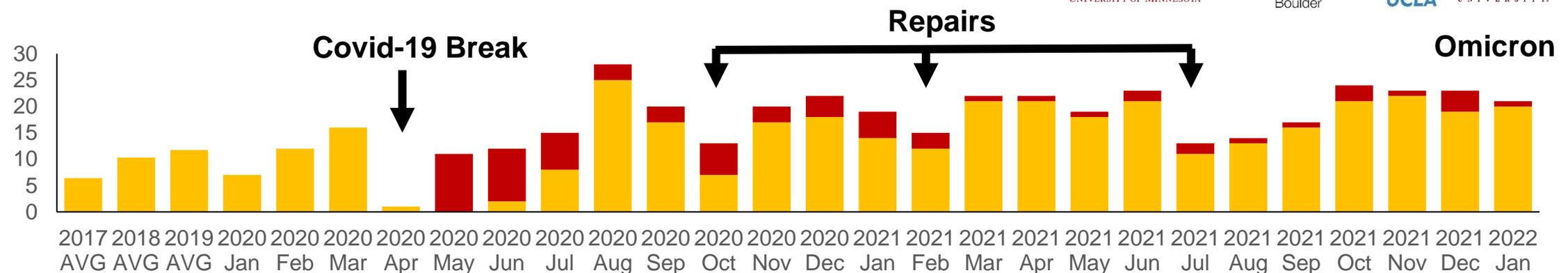
Frederick National Laboratory for Cancer Research

sponsored by the National Cancer Institute

- There are 119 investigators from over 50 institutions
- Over past five years 784 imaging sessions completed.
- There are 64 publications in past five years, with 29 publications over the past year. Rate is increasing.
- Publications are in high-impact journals such as Science, Nature, Nature Communications and elsewhere.



Cancer Projects
 COVID-19 Projects



National Cryo-EM Facility Publications

January 2021 - January 2022

Nanobodies from camelid mice and llamas neutralize SARS-CoV-2 variants

Xu J, ... , Casellas R.
Nature. 2021

Structural basis of ribosomal RNA transcription regulation

Shin Y, Qayyum MZ, ...Murakami KS

Nat Commun. 2021

Structural analysis of cross α -helical nanotubes provides insight into the designability of filamentous peptide nanomaterials

Wang F... Egelman EH, Conticello VP

Nat Commun. 2021

Seesaw conformations of Npl4 in the human p97 complex and the inhibitory mechanism of a disulfiram derivative

Pan M, ... Zhao M

Nat Commun. 2021

A 'Build and Retrieve' methodology to simultaneously solve cryo-EM structures of membrane proteins

Su CC, ... Robinson CV, Yu EW
Nat Methods. 2021

Distinct axial and lateral interactions within homologous filaments dictate the signaling specificity and order of the AIM2-ASC inflammasome

Matyszewski M, ... , Sohn J
Nat Commun. 2021

DPP9 sequesters the C terminus of NLRP1 to repress inflammasome activation

Hollingsworth LR, ... , Wu H
Nature. 2021

Structural mechanisms of TRPV6 inhibition by ruthenium red and econazole

Neuberger A, ... , Sobolevsky AI
Nat Commun. 2021

Cryo-EM structures of engineered active bc1-cbb3 type CIII2CIV super-complexes and electronic communication between the complexes

Steimle S,..., Daldal F
Nat Commun. 2021

Ultrapotent antibodies against diverse and highly transmissible SARS-CoV-2 variants

Wang L, ... , Misasi J
Science. 2021

Cryo-EM structure of the periplasmic tunnel of T7 DNA-ejectosome at 2.7 Å resolution

Swanson NA, ... , Cingolani G
Mol Cell. 2021

Structural mechanism of heat-induced opening of a temperature-sensitive TRP channel

Nadezhdin KD, ... , Sobolevsky AI
Nat Struct Mol Biol. 2021

Mechanistic insight into substrate processing and allosteric inhibition of human p97

Pan M, ... , Zhao M
Nat Struct Mol Biol. 2021

Structures of the mycobacterial membrane protein MmpL3 reveal its mechanism of lipid transport

Su CC, ... , Yu EW
Plos Biol. 2021

Potent neutralizing nanobodies resist convergent circulating variants of SARS-CoV-2 by targeting diverse and conserved epitopes

Sun D Shi Y Nat Commun. 2021

Expression and characterization of SARS-CoV-2 spike proteins

Schaub JM, ... , Finkelstein IJ
Nat Protoc. 2021

SARS-CoV-2 S2P spike ages through distinct states with altered immunogenicity

Olia AS, ... ,Kwong PD
J Biol Chem. 2021

Prestin's conformational cycle underlies outer hair cell electromotility

Bavi N, ... , Perozo E
Nature. 2021

Regulation of MLL1

Methyltransferase Activity in Two Distinct Nucleosome Binding Modes

Ayoub A, ...Dou Y
Biochemistry. 2021

Structural basis of RNA polymerase recycling by the Swi2/Snf2 family of ATPase RapA in Escherichia coli

Qayyum MZ, ... , Murakami KS
J Biol Chem. 2021

Structure of putative tumor suppressor ALDH1L1

Tsybovsky Y, ... , Krupenko SA
Commun Biol. 2022

A molecular mechanism for the generation of ligand-dependent differential outputs by the epidermal growth factor receptor

Huang Y, ... Kuriyan J
Elife. 2021

Structural insights into Ubr1-mediated N-degron polyubiquitination

Pan M, ... , Zhao M
Nature. 2021

Cryo-EM structure of human GPR158 receptor coupled to the RGS7-G β 5 signaling complex

Patil DN, ... , Martemyanov KA
Science. 2021

Structural visualization of de novo transcription initiation by Saccharomyces cerevisiae RNA polymerase II

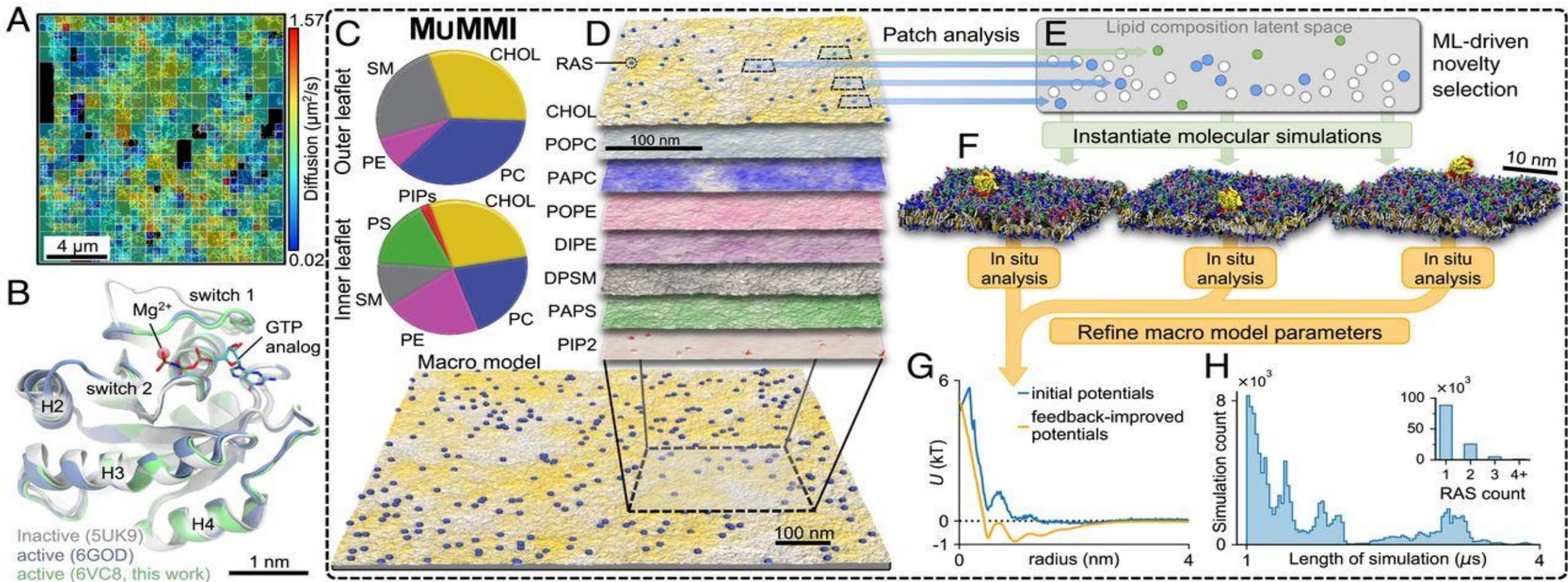
Yang C, ... , Murakami K
Mol Cell. 2022

Molecular mechanism of Arp2/3 complex inhibition by Arpin

Fregoso FE, ... , Dominguez R
Nat Commun. 2022

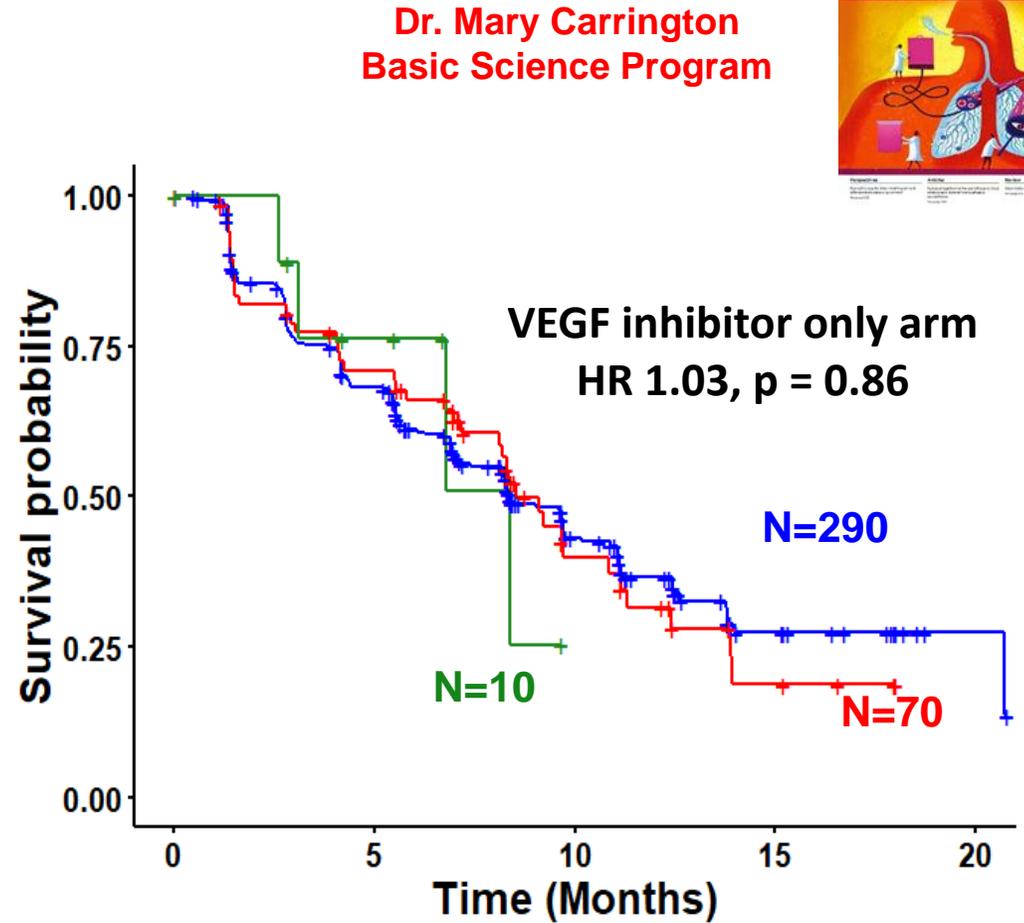
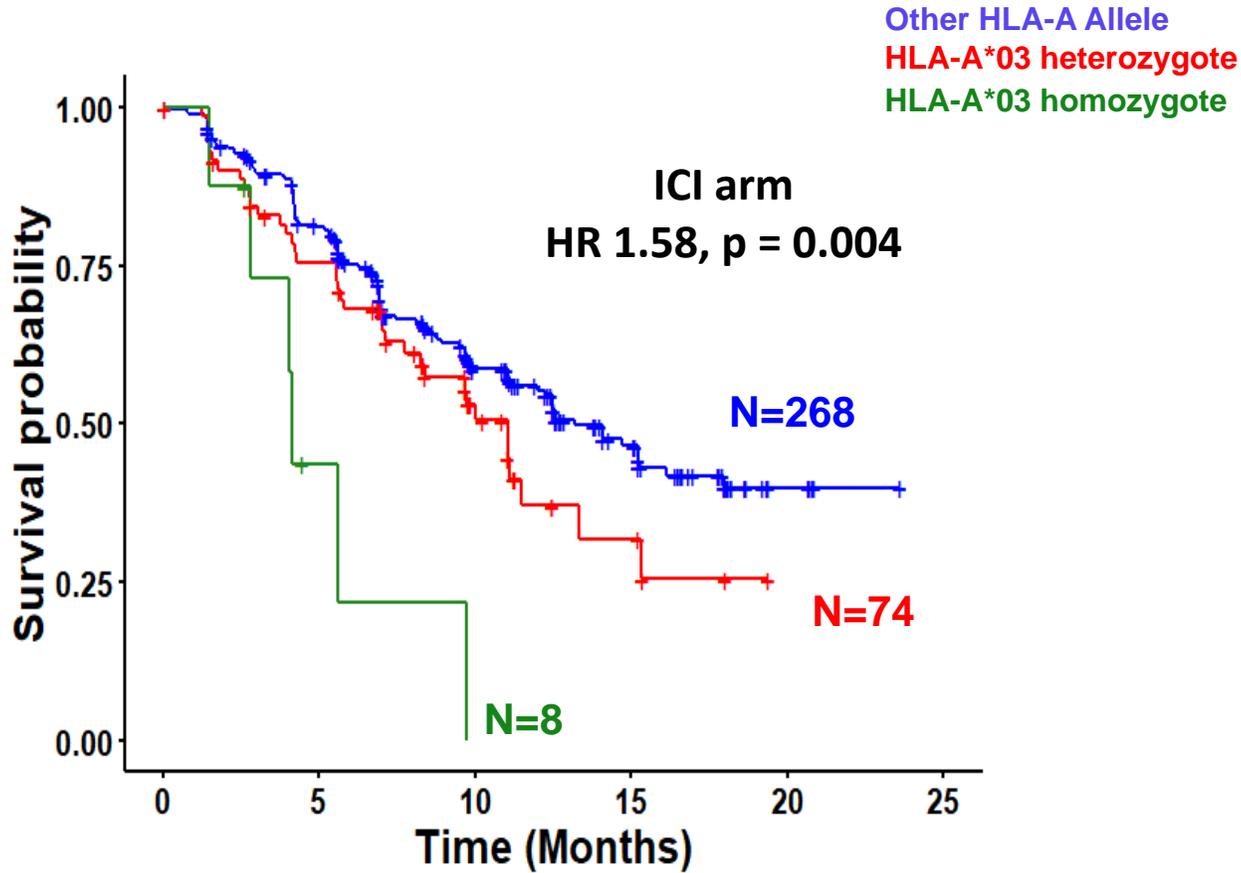
Machine Learning-Driven Multiscale Modeling Reveals Lipid-dependent Dynamics of RAS Signaling Proteins

(A Case Study of Team Science)



Frederick National Laboratory, Lawrence Livermore, Los Alamos and Argonne National Laboratories, IBM, San José State, CRTP, UCSF, and the RAS Initiative.

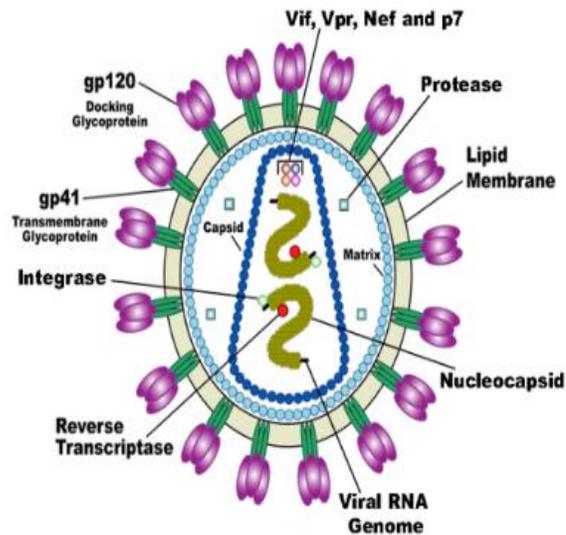
HLA-A*03 Associates with Poor Outcome to Immune Checkpoint Inhibition (ICI) but not Standard-of-Care



Management of Diverse Projects Related to Vaccine Development and Manufacturing

Dr. Jason Gall, VPP
Dr. Kevin Carlton, VPP
Dr. Shanker Gupta, VRC
Dr. John Mascola, VRC
Dr. David Lindsay, VCMP

HIV



Neutralizing
monoclonal
antibody

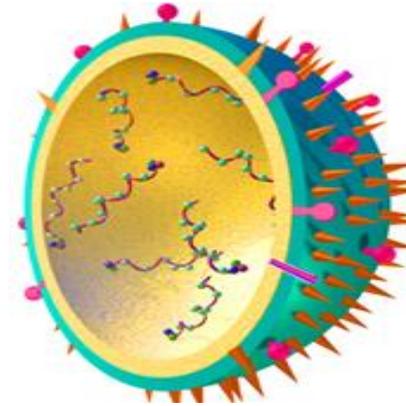
Trimer
vaccine

Filovirus (Ebola)



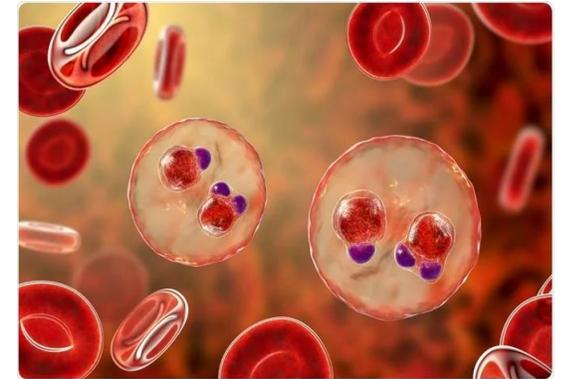
Bispecific
and monoclonal

Influenza



Nanoparticle
Influenza vaccine

Malaria



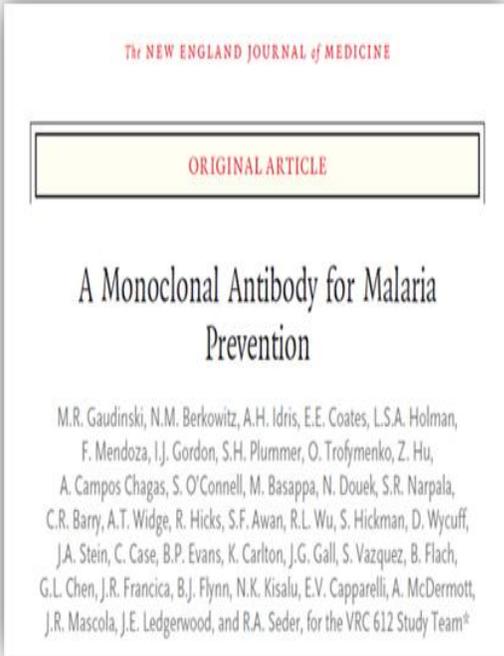
Monoclonal
antibody

VCMP Clinical Manufacturing Support to the Vaccine Research Center

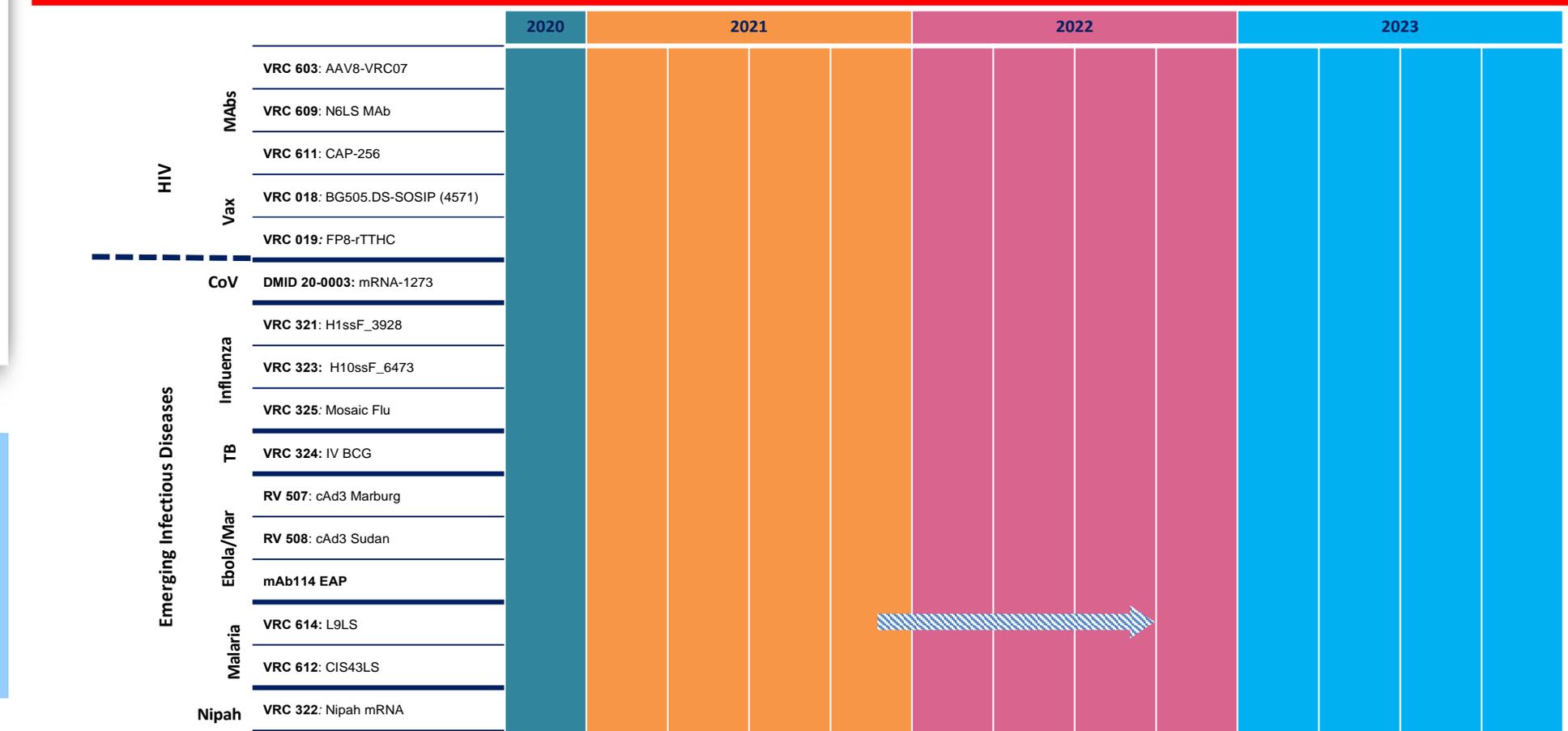
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Dr. David Lindsay in concert with VCMP and VRC/NIAID teams.



Clinical Development Portfolio



- Plasmid DNA (pDNA)
- Monoclonal Antibody (mAb)
- Ferritin-based Nanoparticle
- Pentamer-based nanoparticle
- Recombinant subunit protein
- Synthetic peptide conjugate
- Virus-like particle (VLP)
- Viral vector (cAd3)

International Clinical Trials Training Modules



Leidos Biomedical Research (Beth Baseler and CMRPD) is launching educational modules (at no cost to the government) for extramural investigators in conduct of international clinical trials in resource constrained and politically unstable countries. Trainees will receive CEU or CME credit and a certificate of completion.

Dr. Ian Crozer and Team

Frederick National Laboratory deployed Dr. Crozier (Ebola survivor) to DRC at the request of WHO

MODULES

- Introduction to Clinical Trials (Clinical Trials 101)
- Partnering with international clinical researchers
- Governance Models
- Protocol Development
- Regulatory Approvals and Oversight
- Clinical Trials Monitoring
- Pharmacovigilance
- IT Infrastructure
- Data Management
- Cold-Chain Management
- Inventory management
- Logistics
- Clinical Laboratories
- Biorepository
- Community Engagement/Good Participatory Practices
- Data reporting
- Legal considerations
- Inspections and Audits
- Summary of Lessons Learned

National Cryo-Electron Microscopy Training Program

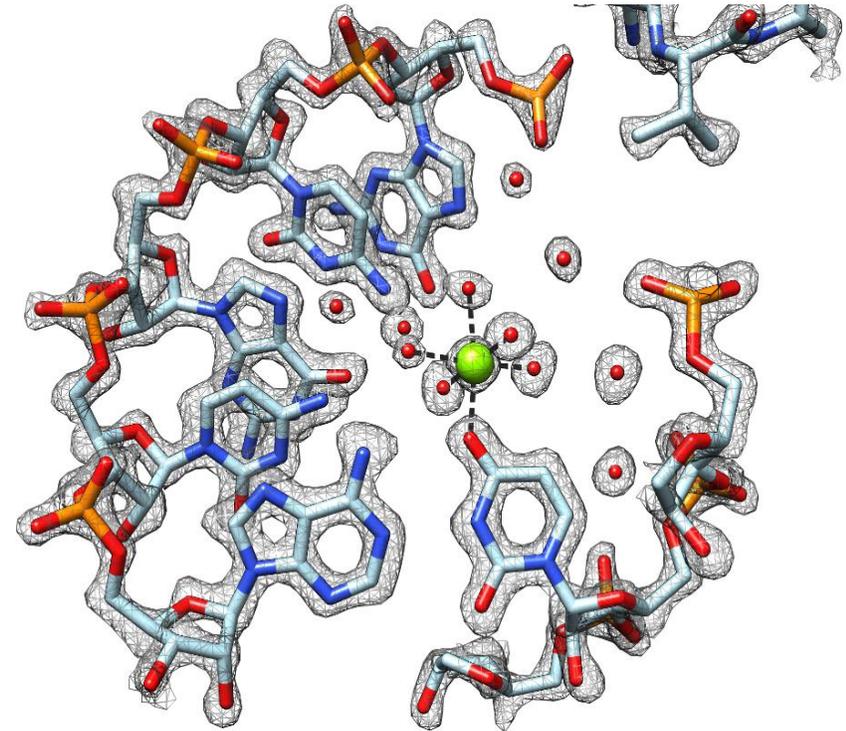
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Frederick National Laboratory is holding a 5-Day Cryo-EM Training Program this summer for novice cryo-EM users.

This workshop is **free to attend** and will be held in-person at the FNLCR's Advanced Technology Research Facility (ATRF).

Twelve attendees will receive classroom learning and hands-on training from FNLCR experts and invited faculty for:

- sample preparation
- grid screening
- data collection and processing
- structure determination
- model building and validation.



Institutions with early stage Cryo-EM programs or plans to create one are encouraged to apply.

Application Process: The Cryo-EM Training application will open **Tuesday, March 15th** through **Friday, April 15th**, and access through FNLCR's Cryo-EM website: [National Cryo-Electron Microscopy Facility | Frederick National Laboratory \(cancer.gov\)](https://www.cancer.gov/nce)

International Day of Women and Girls in Science

**Frederick
National
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National Cancer Institute*



Keynote Speaker

Carla Williams, PhD
Interim Director
Howard University Cancer Center



INSPIRE. MENTOR. CELEBRATE.

Scientific Panelists

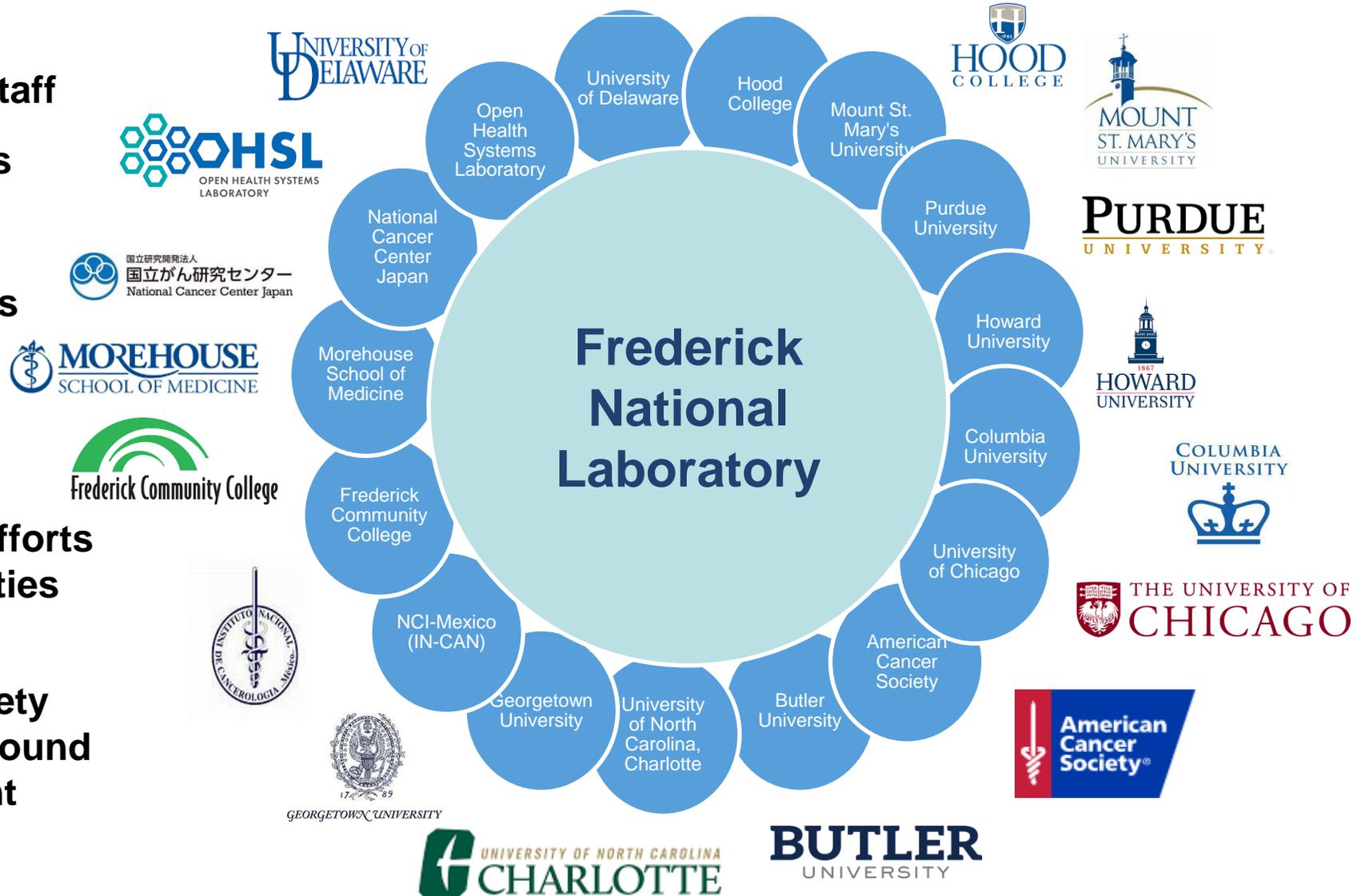
Ruth Nussinov, PhD, FNLCR
Jana Ognjenovic, PhD, FNLCR
Uma Mudunuri, MS, FNLCR
Mary Kearney, PhD, NCI
**Stephanie Mummert, PhD, United States
Patent and Trademark Office**

Frederick National Laboratory Academic Partnerships

Frederick
National
Laboratory
for Cancer Research

sponsored by the
National Cancer Institute

- Appointment and exchange of scientific staff
- Sabbatical opportunities
- Student training
- Postdoctoral fellowships
- Scientific projects
- **Morehouse School of Medicine - partnership around health equity efforts and student opportunities**
- **Howard University – American Cancer Society mentorship, studies around disparities, and student opportunities**



Conclusions

- Reviewed how Frederick National Laboratory rapidly responded to the pandemic.
- Despite this pivot other essential work continued.
- This did not prevent decisive discovery, quantitative biology, translational and clinical science. That scholarship extensively engages the extramural biomedical community.
- Our public-private partnership and educational efforts seek to advance the public's health.